Where permitted, 23andMe provides customers with reports about genetic variants that have a strong effect on health-related phenotypes. These reports fall under three categories: Drug Response, Inherited Conditions, and Genetic Risk Factors (GRFs). This document describes, for each report type, how we identify genetic variants for inclusion and how we communicate information about these variants.

1 Report Types

1.1 Drug Response
Drug Response reports cover genetic variants known to affect response to certain drugs and medications. Differences in response may include rate of metabolism, risk of side effects, and overall efficacy.

1.2 Inherited Conditions

Inherited Conditions reports cover variants that typically follow a strict recessive inheritance pattern. Environmental factors do not usually play a role in whether or not a person has the condition, though they may affect severity or symptoms. Carriers (individuals with one copy of a disease-causing variant) generally do not have the disease, while individuals with two disease-causing variants (either two copies of the same variant or two different variants in the same gene) generally have the disease.

1.3 Genetic Risk Factors (GRFs)

Genetic Risk Factor (GRF) reports cover variants that have a strong effect on disease risk but are of lower penetrance than variants in Inherited Conditions reports. For many of the reports in this category, having a single copy of the variant is associated with elevated risk of disease. The variants in this category can be interpreted independently of other genetic markers, but risk for the condition is usually also influenced by lifestyle, environment, or family history.

2 Criteria

For a genetic marker to be eligible for inclusion for any of the report types described, it must satisfy certain analytical and scientific criteria. Analytically, markers must be on the most recent version of our genotyping platform. They must also demonstrate high genotyping quality.

Markers should also have a well-established and meaningful effect on the condition of interest. The specific scientific criteria for a marker vary by report type, as described below. Exceptions may be made to these requirements for all categories, especially for rare conditions or markers restricted to very specialized populations, if 23andMe scientific consensus concludes that the overall strength of the evidence is sufficient.

2.1 Drug Response

A genetic marker is eligible if one of the following is true:

- Specific clinical practice guidelines exist for the marker, including recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) or other clinical organizations or working groups.
- Specific information in the drug’s labeling or documentation from regulatory agencies acknowledges the impact of the genetic marker on drug response.

A genetic marker is potentially eligible if all of the criteria below are satisfied:
• 23andMe scientific consensus concludes that there is meaningful interpretation of a positive result for the genetic marker or corresponding allele.
• At least three scientific or clinical references exist that show the marker has a consistent clinical effect, at least one of which provides evidence for the functional mechanism by which the marker affects drug response.

2.2 Inherited Conditions

A genetic marker is eligible if the following are true:
• The marker is considered highly penetrant for the condition and follows a recessive mode of inheritance.
• Carrier screening guidelines specific to the marker have been published by the American College of Medical Genetics or other established medical organizations.

A genetic marker is potentially eligible if at least three scientific or clinical references exist supporting a pathogenic role for the marker, at least one of which provides evidence for a functional disease mechanism. The existence of other genetic tests for the condition that include the marker may support the marker’s eligibility.

2.3 Genetic Risk Factors (GRFs)

A genetic marker is eligible if there are clinical practice guidelines from established medical organizations that include the marker.

A genetic marker is potentially eligible if multiple criteria below are satisfied:
• 23andMe scientific consensus concludes that there is meaningful interpretation of a positive result for the genetic marker or corresponding allele.
• At least three scientific or clinical references exist supporting a consistent effect for the marker, at least one of which provides evidence for a functional disease mechanism.
• Other genetic tests that include the marker exist for the condition.

If a risk estimate is reported, at least one of the following should also be true for at least one marker genotype:
• The odds ratio (OR) associated with at least one genotype should be at least 3.5.
• The relative risk (RR) associated with the genotype should be at least two-fold.
• The penetrance associated with the genotype should be greater than 20%.

If multiple studies report quantitative measures of risk, preference should be given to studies which are better powered to detect associations (usually larger
and more recent studies) when assessing whether the marker meets the specified cutoffs.

3 Reporting

We report several types of categorical outcomes. For Inherited Conditions and GRFs, the primary outcome reported is the presence or absence of the genetic variant(s). For Drug Response, the primary outcome reported may be either the predicted phenotypic response or the predicted enzymatic variant, as applicable.

For Drug Response and GRFs, additional information about risk associated with a result may be reported if available and supported by literature. This risk may be reported as a qualitative (e.g. higher risk) or quantitative (e.g. 45% lifetime risk, 6 times higher odds) measure. When reporting a quantitative measure, preference will be given towards risk measures that are more intuitive. Lifetime risks are preferred to relative risks, and relative risks are preferred to odds ratios. Any quantitative measures of risk (e.g. odds ratios, lifetime risks) reported require at least one large supporting study or multiple smaller studies.

3.1 Ancestry-Based Reporting

Because all variants discussed here are considered causal or functional, the association with the condition of interest (but not quantitative measures of effect) should be considered valid for all ancestry groups. However, if the marker reported is only a tag for the causal variant, the use of the tagging marker may not be valid for ancestry groups other than the one in which the tagging studies were conducted.

Since the effect size associated with the marker can vary between populations, such quantitative measures may not be valid in ancestry groups other than those studied. Quantitative risk estimates for each additional population must be supported by a population-specific study.

3.2 Multi-Marker Reports

Reports for many conditions include more than one marker. These markers may or may not be in the same gene.

In order to report a quantitative measure of risk for a particular combination of markers, that exact combination must have been studied in the literature. For example, a published risk estimate for a combination of F5/F2 markers may be reported directly, but risk estimates for individual F5 and F2 markers cannot be combined into a single quantitative measure of risk.

For people who are positive for different markers in the same gene, we assume that the two variants are typically inherited on separate alleles, unless there is empirical evidence that they can be inherited together.
In some cases, an individual may not have genotype data at all markers used in a report. If such an individual has a positive result at one of the other markers, that result will still be reported. The positive result may be accompanied by language indicating that we were not able to determine a genotype at all markers.

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